DERIVATIVES OF PIPERAZINE AND MORPHOLINE. I. ADDITION TO ALPHA, BETA-UNSATURATED KETONES

By

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A Dissertation Presented to the Graduate Council of
The University of Florida
In Partial Fulfilment of the Requirements for the
Degree of Doctor of Philosophy

UNIVERSITY OF FLORIDA
June, 1937

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REVIEW OF LITERATURE AND INTRODUCTION

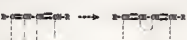
There are but two possible results from the interaction of two compounds: (1.) two or more new kinds of molecules may be formed from the two original species of molecules; or, (2.) the two molecules may combine to form a new, single substance. The latter case comprises our conception of "addition reaction", and constitutes the subject of this research.

It is not surprising that such important reactions should have resulted in a great number of hypotheses endeavoring to explain their nature. Although it is impossible to include here a complete discussion of these theories, it becomes pertinent to outline some of the various explanations which have been proposed.

Perhaps the most general view is that promulgated by Michael[1] in his "distribution principle". Addition is explained by him as the result of the affinity of the two interacting molecules for each other, and occurs in such a way as to produce the most "chemically saturated" molecule. This "neutralization of affinity" is assumed to depend principally upon the nature of the atoms comprising the two interacting molecules.

The hypothesis presented by Vorlander, et al.[2,3,4] maintains that the criterion which determines that an addition compound be formed is a difference between the two interacting molecules, which he termed a "difference in potential". The greater the difference in potential between them, the more rapid will be the coalescence; hence, the "difference in potential may be determined by measuring the velocity with which the two substances combine". Supposedly, there is first formed, almost instantaneously, an unstable product; this product may undergo a change and be converted into a stable product whose heat of formation is measurable. It is logical to assume that with the formation of the stable products the strain is less than is the case of the labile compounds.

Thiele[5], in his classical work published in 1899, pointed out the stability of unsaturated systems containing two double bonds separated by one single bond. This type of unsaturated system is referred to by the terms "conjugation" or "conjugate system", and it is the additions to compounds included in this classification which form the nucleus of the present research. In such systems the unsaturation is limited almost wholly to the two outside atoms of the chain, while the two center atoms are nearly completely saturated. The Thiele theory is based upon the assumption that, in the case of a double bond between two atoms, the whole of the affinity is not used up, but in addition to that which is used in holding the atoms together there is a slight excess which he termed "residual affinity" or "partial valency". Whenever the double bonds occur in alternate positions, the residual affinities of the two central atoms result in a mutual saturation. This conception of partial valencies is represented by dotted lines, as follows:



Griner[6], in 1892, investigated the addition of bromine to butadiene, which is a typical conjugate system. Since this compound contains an alternate pair of double bonds, it is to be expected that it could unite with four atoms of bromine simultaneously, or at least take up two atoms of bromine at one of the double bonds, as follows;

$$Br\text{-}CH_2\text{-}CHBr\text{-}CH{=}CH_2 \quad \text{or} \quad Br\text{-}CH_2\text{-}CHBr\text{-}CHBr\text{-}CH_2\text{-}Br$$

Griner reported that there was first formed a liquid dibromide which soon changed into a solid, melting point 53-54° C. Thiele[7], proved that this solid is a 1,4-dibromobutene-2, which contains a double bond in the center of the chain;

$$Br\text{-}CH_2\text{-}CH{=}CH\text{-}CH_2\text{-}Br$$

Willstatter and Bruce[8], showed that the migration of these bonds is a reversible one, since upon treatment of the dibromide with potassium hydroxide, there is generated a 1-bromobutadiene in which the double bonds are again located in the 1,2-positions. More recently, Farmer, Lawrence and Thorpe[9], have confirmed Griner's report that a liquid dibromide is first formed. They have shown that this is a 1,2-dibromobutene-3, which changes reversibly at 100° C. into a 1,4-dibromo-butene-2, and results in an equilibrium mixture containing 20% of the former and 80% of the latter.

The present research deals more specifically with additions to alpha, beta-unsaturated ketones. Thiele has shown that in such cases, where two different types of double bonds are conjugated with each other,

addition agents such as hydrogen and hydrogen cyanide will add to the ends of the conjugated chain; a subsequent transformation from the enol to the keto form may occur:

$$CH_2=CH-CH=O \quad + \quad HCN \dashrightarrow CN-CH_2-CH=CH-OH \dashrightarrow CN-CH_2-CH_2-CHO$$

When we thus combine two different types of unsaturation in a single molecule it becomes interesting to observe the reaction of agents which are capable of acting upon both the carbonyl group and the ethylenic linkage. Ammonia is such an agent, but when it reacts with mesityl oxide, a typical alpha, beta-unsaturated ketone, it attacks only the ethylenic linkage, leaving the carbonyl group intact:

$$(CH_3)_2C=CH-CO-CH_3 + NH_3 \dashrightarrow (CH_3)_2\underset{\displaystyle NH_2}{\underset{|}{C}}-CH_2-CO-CH_3$$

Hydroxylamine, on the other hand, yields two different products according to the conditions. Harries, et al.[10,11,12], observed that when the reaction is carried out in methanol solution in the presence of sodium methylate, the principal product results from the 1,4-addition of hydroxylamine, with subsequent rearrangement:

$$(CH_3)_2C=CH-CO-CH_3 + NH_2OH \dashrightarrow (CH_3)_2\underset{\displaystyle NH-OH}{\underset{|}{C}}-CH_2-CO-CH_3$$

However, if hydroxylamine hydrochloride is neutralized stoichiometrically with sodium carbonate and then reacted with mesityl oxide in ethanol solution, the expected carbonyl group reaction occurs and mesityl oxime is formed;

$$(CH_3)_2C{=}CH{-}C(NOH){-}CH_3$$

It is apparent that in neutral solution the carbonyl group is the more reactive, but in alkaline solution the ethylenic group becomes activated and additions to it are facilitated.

One of the unique characteristics of conjugate systems is the transmission of chemical reactivity from one atom to another. On the preceding page it has been shown that when ammonia adds to mesityl oxide it does not react with the carbon atom of the carbonyl group, but rather, with the carbon atom at the other end of the conjugated chain; the fact that this atom is a constituent of the conjugated chain causes it to be possessed of an unusual reactivity. Similarly, the hydrogen adds to a carbon atom instead of the oxygen atom of the carbonyl group. It is a moot question whether such additions, and the addition of bromine to butadiene, take place in the 1,4-position with subsequent rearrangement to the 1,2-position, or vice versa. However, it is important to note that there is an alternation of affinity, and that alternate atoms apparently acquire a similar polarity and a similar reactivity.

Lapworth[13], in 1898, proposed that in each intramolecular rearrangement the labile group is transferred from the alpha-atom to the gamma-atom, and that "a labile group might move along a chain of alternately single and doubly-bound atoms, the ethylenic and single linkings changing places in the path of the labile group". This hypothesis, which attributed analogous properties to only the alternate atoms in the chain, opened up a new perspective of conjugation and furnished a foundation for all subsequent investigations in this field.

The symbols which Thiele utilized in interpreting his theory of partial valencies are not in accordance with and cannot be converted directly into the symbols which are used in the modern electronic interpretation of valence. Kuhn, et al.[14,15], have done a considerable amount of work in the mechanism of these notations, but the simplest electronic interpretation of conjugated systems is that proposed by Lowry[16] in 1923, in coalition with the theory of polar activation of covalent bonds. He proposed that the only molecules which undergo chemical change are the activated ones, and that addition reactions of olefines under the influence of polar reagents are dependent upon the ionization of one of the links of the double bond:

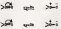
$$-C{=}C- \dashrightarrow -\overset{+}{C}-\overset{-}{C}-$$

It is a characteristic property of conjugate systems to develop a series of positive and negative charges on alternate atoms as a result of the activation by the double bonds:

$$-C{=}C-C{=}C- \dashrightarrow -\overset{+}{C}-\overset{-}{C}-\overset{+}{C}-\overset{-}{C}- \quad \text{or} \quad -\overset{-}{C}-\overset{+}{C}-\overset{-}{C}-\overset{+}{C}-$$

In the dormant form of the molecule there is a complete alternation of single and double bonds, but in the activated form these are converted into a series of atoms bearing alternately positive and negative charges. This interpretation, in which ionic charges of like sign are developed by alternate atoms, is entirely in accordance with the hypothesis of Lapworth.

In many cases, additions to unsaturated compounds have been attributed to a polar activation of the double bond[17]. This is brought about under the influence of an ionic reagent, and gives rise to an unstable semi-polar bond;



The arrows indicate that, as a result of the process of activation, a pair of shared electrons becomes transferred from the double bond to the atom of carbon or oxygen which acquires a unit negative charge in the activated product. In the unsaturated aldehydes and ketones the sign of the charges is determined by the tendency of the oxygen to acquire a negative charge, and not the carbon atom; thereby the oxygen atom at the end of the chain becomes negative, and the remaining carbon atoms alternately positive and negative:

A more detailed discussion of the electronic interpretation of conjugation cannot be presented within the limits of this discussion; however, the material herein presented is sufficient to indicate that conjugate systems possess the property of undergoing a rearrangement of bonds in such a way that a valency electron is transferred progressively from one end of the chain to the other. This provides for the neutralizing of the opposite charges of an ionized reagent in both the 1,2- and 1,4-additions, and provides a mechanism for the transposition of a 1,2-addition into the isomeric 1,4-addition.

Thiele's original classification of conjugate systems included only those containing ethylenic and carbonyl groups. Robinson[18] and Becker[19], have shown that any element, for examples nitrogen and sulfur, which is capable of forming a double covalent bond, or which possesses unshared electrons, may form an integral part of a conjugate system. Robinson[20], succeeded in classifying such systems into sharply defined groups, since their reactions are largely dependent upon the electrical nature of the atoms which are present. His classification is as follows: (1.) poly-enoid systems, (2.) hetero-enoid systems, (3.) katio-enoid systems, (4.) neutralized systems, (5.) discordant polar systems. On the basis of this classification, alpha, beta-unsaturated ketones, which are the subject of this research, belong in the katio-enoid systems. These systems contain hetero-atoms which tend to abstract electrons, and in so doing produce carbon kations. Rearrangement of valency electrons occurs in the following manner:

Rearrangement of the valency electrons in these systems is conditioned by the fact that the hetero-atom (oxygen) forms a more stable anion than the carbon atom.

The effect of substituent groups upon additions to double bonds was investigated by Nef[21] in 1899; he concluded that it is possible to retard addition reactions in this manner. Later, Bauer[22] undertook similar investigations and succeeded in verifying Nef's conclusion. He observed that if carboxyl, carbethoxyl, or phenyl groups, or bromine atoms are accumulated in the vicinity of a double bond, bromine does not readily add. For example, bromine does not add to tribromacrylic acid,


$$Br\text{-}\underset{Br}{C}{=}\underset{Br}{C}\text{-}COOH$$

nor to dibromo-crotonic acid,


$$CH_3\text{-}\underset{Br}{C}{=}\underset{Br}{C}\text{-}COOH$$

although both contain double bonds.

The investigations of Bauer, et al.[23,24], also showed that when nitrile, carbethoxyl, and phenyl groups are placed in the vicinity of a double bond, the retard upon the addition of bromine is in the order: nitrile carbethoxyl phenyl. The influence of the phenyl group is also conditioned by substituents on it; it is weakened by nitration, although a nitro group in the ortho-position has the least effect, and one in the meta-position the most effect. Furthermore, he was able to show that the addition of bromine to double bonds is reversible, and that the equilibrium which is obtained at various stages is dependent upon the substituents in the molecule. Noteworthy is the fact that there is a remarkable correlation between the effect of substituents on the addition of bromine and their influence upon the dissociation constant of acids.

A review of the literature reveals a decided lack of investigations concerning the influence of substituent groups upon the additions to conjugate systems, and especially alpha, beta-unsaturated ketones. It is with the object of elucidating this problem that the present research has been undertaken. The present theories and mechanical hypotheses are quite insufficient, and a virgin field awaits the theorist.

Tambor and Wildi[25] found that benzalacetophenone combines with alcoholic ammonia in the cold to give the compound,

$$\begin{array}{l} \phi\text{-}CH\text{-}CH_2\text{-}CO\text{-}\phi \\ \quad | \\ \quad NH \\ \quad | \\ \phi\text{-}CH\text{-}CH_2\text{-}CO\text{-}\phi \end{array}$$

In a similar manner addition compounds of benzalacetophenone with several primary aromatic amines were prepared. They were not successful in adding secondary aromatic or mixed secondary bases. The addition goes readily in the cold, generally with or without alkali. Generally the addition does not occur in one day. Two moles of benzalacetophenone add one mole of ammonia, one mole of nitrotoluidine ($CH_3:NH_2:NO_2 = 1:2:5$), one mole of m-nitraniline, or one mole of alpha-naphthylamine; however, equimolecular quantities of the ketone combine with aniline, p-toluidine, and beta-naphthylamine. These compounds are pure white; however, the introduction of a chromophore group (e.g., nitro group) into the molecule results in a color change to red or yellow.

It is noteworthy that Tambor and Wildi added p-toluidine to benzalacetophenone, but were unsuccessful in adding o-toluidine; apparently the position of substituents on the benzene rings does affect the addition. Although these compounds were found to be stable under ordinary conditions, it is stated that by attempting to acetylate benzalacetophenone aniline, or by short warming, total decomposition occurred.

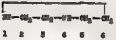
Georgi and Schwyzer[26] attempted to add d-fenchone to benzalacetophenone by mixing in alcohol with sodium hydroxide. The expected reaction did not occur and instead, dibenzaltriacetophenone, $\phi CH(CH_2COCH_2-\phi)_2$, melting point 197°, was formed. When piperidine was used, piperidobenzylacetophenone,

was obtained in the form of yellowish red crystals, melting point 94° C. Upon heating with water it decomposed into the original substances; however, the hydrochloride, melting point 183-184° C., was prepared. Fenchone and anisalacetophenone in the presence of alkali do not condense, and piperidoanisalacetophenone is too unstable to be isolated.

NOMENCLATURE

Several systems of nomenclature for piperazines and chalcones occur in the literature. However, it seems expedient to utilize throughout this discussion the systems adopted by Chemical Abstracts.

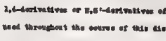
The official Chemical Abstracts formula for piperazine is:



$NH-CH_2-CH_2-NH-CH_2-CH_2$

Derivatives in which the substituent groups are attached to the nitrogen atoms are termed 1,4-derivatives or N,N'-derivatives of piperazine. The former system is used throughout the course of this discussion.

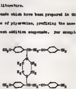
The formula given by Chemical Abstracts for chalcone is:



The positions of substituents on the benzene rings are indicated by the proper numerals. Substituents on the ethylenic carbon atoms are indicated by the Greek letters alpha and beta. In the older literature chalcones are named according to the aromatic aldehydes and ketones from which they are prepared, using either numerals or the terms ortho, meta, and para to indicate the positions of substituents on the benzene rings. For example,

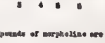
may be termed anisal p-chloroacetophenone or 4-chloro-omega-(4-methoxy-benzal)-acetophenone. Because of its lack of brevity and lucidity this system is not used in the present discussion; however, it is frequently encountered in the literature.

The compounds which have been prepared in this research are named as derivatives of piperazine, prefixing the name of the chalcone as is customary with such addition compounds. For example,



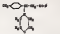
is termed 1,4-Bis-(4-methoxy-4'-methyl-chalcone) piperazine.

The official Chemical Abstracts formula for morpholine is:



$$\overbrace{O-CH_2-CH_2-NH-CH_2-CH_2}$$

The addition compounds of morpholine are named as derivatives of morpholine, prefixing the name of the chalcone as was done in the case of the piperazine addition compounds. For example,



is designated 4-(4-Methyl-chalcone) morpholine.

THEORETICAL DISCUSSION

The object of this investigation, as outlined in the foregoing pages, is to study the effect of substituent groups upon additions to alpha, beta-unsaturated ketones. Since unsaturated ketones of the aromatic series offer a greater variety of substitutions than those of the aliphatic series, the investigation is limited chiefly to this group. In order to make a comparison of results, only two addition agents were used throughout the course of the research. The heterocyclic secondary diamine, piperazine, and the heterocyclic secondary amine ether, morpholine, were chosen for two reasons: (1.) additions of these compounds are unrecorded in the literature; and (2.) the compounds which should result from such additions would be similar in structure to certain hypnotics and anesthetics, and should prove to be interesting in their physiological action.

With few exceptions, unsaturated ketones cannot be purchased, so it became necessary to prepare most of the intermediates used in the investigation. Since much of the data in the literature is erroneous and could not be reproduced, a detailed account of the preparation of these compounds is presented in the section entitled, "Preparation of Intermediates".

Unsaturated ketones of the aromatic series are most readily prepared by the classical Claisen reaction. Equi-molecular quantities of the corresponding aromatic aldehyde and aromatic ketone were dissolved in a suitable quantity of 95% ethanol. One hundred grams of a 10% aqueous solution of sodium hydroxide per mole of aldehyde (or ketone) was then added. The solution was thoroughly stirred, and the alpha, beta-unsaturated ketone generally separated out almost immediately; in most cases it was in the form of a pale yellow solid. It was filtered with suction, air-dried, and then recrystallized from commercial heptane or 95% ethanol, depending upon the specific nature of the compound. Most of the alpha, beta-unsaturated ketones used in this investigation are chalcones, and their preparation may be indicated by the following type reaction:

$$Ar\text{-}CHO \quad + \quad H_3C\text{-}CO\text{-}Ar' \quad \xrightarrow[\text{dil. NaOH}]{} \quad Ar\text{-}CH{=}CH\text{-}CO\text{-}Ar' \quad + \quad H_2O$$

where Ar and Ar' represent any aryl (substituted benzene) groups.

The addition of piperazine to the alpha, beta-unsaturated ketones thus prepared was found to be best effected by refluxing the reactants in toluene solution. Contrary to the findings of Harries, et al. [10,11,12], alkali did not appear to facilitate the reaction. In general, the procedure was to dissolve one mole of anhydrous piperazine in boiling toluene under reflux; as soon as solution was complete, a toluene solution of two moles of the alpha, beta-unsaturated ketone was added. The solution was then refluxed over a free flame for ten hours. Although in most cases a shorter reflux-time could have proved sufficient, this period of time was deemed ample for all additions and was used throughout for the sake of consistency. The solution was then allowed to stand in the ice box for at least one day; in some cases, where the product was slow in separating, it was allowed to stand longer. Generally, the addition compound separated out in the form of minute, white or yellowish crystals. These were filtered off from the toluene with suction, washed with a small amount of 95% ethanol to remove the toluene, and then washed with a large amount of water in order to remove any unreacted piperazine. The compound was then air-dried.

The yields of the crude products varied from 70% to 95%, but in most cases approached the latter value. Toluene was found to be best suited as a recrystallizing solvent; generally it was necessary to recrystallize the addition compound at least three times before subsequent recrystallizations gave no increase in melting point. The pure product in most cases was in the form of minute, pure white crystals. A considerable loss of product was incurred in the recrystallizing process, and the yields of the purified products dropped to about one-third of the per cent yield of the crude products. However, a more suitable solvent could not be found, and it was desirable to utilize only the highly purified products for analyses.

Carbon and hydrogen determinations were carried out by the combustion method in the case of the parent compound, 1,4-bis-chalcone piperazine, in order to definitely establish its composition. The nitrogen content was determined also, by means of the Kjeldahl method. Analytical data for the other addition compounds were confined to nitrogen determinations, since these were considered sufficient to characterize the individual compounds.

Addition of piperazine to chalcones probably occurs in the usual manner of additions to alpha, beta-unsaturated ketones. Piperazine adds to the two end partial valencies (1,4-positions) to give the enolic form (I) of the addition compound, where Ar and Ar' are aryl groups:

the enolic form, being unstable, is rapidly converted to the keto form (II), with which it then exists in reversible equilibrium:

(I) (II)

When equilibrium is reached, the major portion of the compound exists in the stable keto form (II), and the resultant product is effectively a 1,2-addition compound. Although a mono-addition compound,

and various stereo-isomers are theoretically possible besides the bis-addition product, only the latter compound was isolated in each case.

The cases in which addition has been effected are indicated in the experimental tables; a great variety of substituted chalcones have undergone addition with piperazine. Chalcones bearing methyl, methoxy, nitro, chloro and bromo groups on either or both benzene rings have undergone addition. The position of the substituent group on the ring apparently has no determinative effect.

The experimental section entitled, "Negative Reactions with Piperazine", indicates the alpha, beta-unsaturated ketones which did not yield addition compounds under the experimental conditions which were successful with the foregoing compounds.

From the nature of these compounds it is to be expected that they display a limited solubility in most solvents. They are insoluble in water, alcohol, ether, and hydrochloric acid; slightly soluble in cold benzene and toluene, and fairly soluble in the hot solvents. They are moderately soluble in halogenated solvents such as chloroform, chlorobenzene and ethylene dichloride.

The compounds are all stable under ordinary conditions, and are not decomposed by heating with water as is the case with the piperidine additive compound reported by Georgi and Schwyzer[26]. When 1,4-bis-chalcone piperazine was heated with hydrochloric acid it was completely decomposed into piperazine dihydrochloride and chalcone. A similar decomposition occurred when dry hydrogen chloride was passed into a chloroform solution or hot toluene solution of the compound; hence, a hydrochloride of the compound was not isolated. When a toluene solution of

1,4-bis-chalcone piperazine was refluxed with ethyl iodide, decomposition again occurred instead of the expected formation of the quaternary ammonium base,

A small amount of a pale brass compound separated from the hot solution. This was filtered off and recrystallized from n-butanol; mixed melting points showed it to be identical with the product obtained by refluxing ethyl iodide with piperazine in toluene solution. The filtrate was evaporated to dryness on a steam-bath, leaving a pale yellow compound, which was recrystallized from 85% ethanol. Mixed melting points proved it to be the unsaturated ketone, chalcone. These decompositions are perhaps surprising, since the unsaturated ketone results; however, further reflection reveals that this is entirely analogous to the usual degradation of amines, whereby the alkyl group is split off as an unsaturated hydrocarbon.

The addition of morpholine to the alpha, beta-unsaturated ketones was found to be best effected by refluxing an excess of morpholine with the ketone in commercial heptane. In general, the procedure was to dissolve two-tenths mole of the ketone in a minimum amount of boiling commercial heptane under reflux; as soon as solution was complete three-tenths mole (one-tenth mole excess) of anhydrous morpholine was added.

The solution was then refluxed over a free flame for ten hours, as was done in the addition of piperazine. The solution was allowed to stand in the ice box one or ten days, whereupon the addition compound separated out in the form of pure white, needle-like crystals. These were filtered off from the heptane with suction, washed with a small amount of 95% ethanol to remove the heptane, and then washed with a large amount of water in order to remove any unreacted morpholine. The compound was then air-dried.

The yields of the crude products were very nearly quantitative, all being well over 90%. Commercial heptane was found to be best suited as a recrystallizing solvent; generally it was necessary to recrystallize the addition compound at least three times before subsequent recrystallizations gave no increase in melting point. The pure product in all cases was in the form of pure white, needle-like crystals. No appreciable loss of product occurred in the recrystallizing process, but it was considered advisable to submit the compounds to repeated purification before analyzing them.

Analytical data for the morpholine addition compounds was confined to nitrogen determinations by the Kjeldahl method, since the nature of the addition was sufficiently proved in the addition of piperazine.

The mode of addition of morpholine to the alpha, beta-unsaturated ketones is undoubtedly quite analogous to the addition of piperazine, involving a 1,4-addition with a subsequent enol-keto rearrangement to give the 1,2-addition product. However, in the case of the morpholine addition, one mole of morpholine and one mole of the unsaturated keare involved. The cases in which addition has been effected with morpholine are indicated in the experimental tables. Chalcones bearing methyl, methoxy, chloro and bromo groups on either or both benzene rings have undergone addition. Here again, the position of the substituent group on the ring apparently has no determinative effect.

The experimental section entitled, "Negative Reactions with Morpholine", indicates the alpha, beta-unsaturated ketones which did not yield addition compounds under the experimental conditions which were successful with the foregoing compounds. In many cases the addition compound apparently was formed, but was so unstable that attempts to purify it resulted in complete decomposition to morpholine and the unsaturated ketone.

Solubility properties of the morpholine addition compounds are quite dissimilar to those of the piperazine compounds. They are insoluble in water, but soluble in alcohol, toluene, chloroform and acetone, and very soluble in dilute hydrochloric acid. They are slightly soluble in cold commercial heptane, and readily soluble in the hot solvent.

Under ordinary conditions the compounds which were isolated are quite stable. However, like the piperidine compound reported by Georgi and Schwyzer[26], and unlike the piperazine addition compounds, they are decomposed by heating with water; the decomposition results in morpholine and the unsaturated ketone. Treatment with hydrochloric acid results in a similar decomposition.

EXPERIMENTAL TABLES AND PROCEDURES

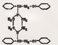
A. Addition Compounds of piperazine

1. Preparation of 1,4-Bis-chalcone piperazine.

Seventeen and two-tenths grams (0.2 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 83.2 grams (0.4 mole) of chalcone (benzalacetophenone) was then added. The total volume of the solution was about 300 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a copious, white precipitate resulted. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and recrystallized from toluene three times, yielding minute, pure white crystals. These were washed with ether after the final recrystallization, in order to remove the toluene. The yield of crude product was 97.7 grams (98% of theoretical) and the yield after three recrystallizations was 88.2 grams (88% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.58% N. Calculated: 5.57% N. Carbon analysis gave 81.08% C. Calculated: 81.23% C. The hydrogen analysis gave 6.79% H. Calculated: 6.82% H. The corrected melting point of the pure compound was 188.0-189.2° C.

1. 1,4-Bis-chalcone piperazine.

Empirical Formula	$C_{34}H_{34}O_2N_2$	
Structural Formula		



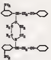
Molecular Weight	502.67	
Melting Point	185.0-186.0° C.	
Yield of Crude Product	90%	
Yield after Three Recrystallizations	82%	
Analyses	Found	Calculated
Nitrogen	5.59%	5.57%
Carbon	81.06%	81.23%
Hydrogen	6.79%	6.82%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Very soluble	
Chlorobenzene	Soluble	

C. Preparation of 1,4-Bis-(3-nitro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 25.3 grams (0.1 mole) of 3-nitro-chalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized once from about 1½ liters of toluene. This yielded a pale yellow, crystalline compound, which became light brown upon standing in a desiccator. The crystals were washed with ether after the final recrystallization in order to remove the toluene. The yield of crude product was 25.7 grams (87% of theoretical) and the yield after one recrystallization was 8.0 grams (27% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 9.45% N. Calculated: 9.46% N. The corrected melting point of the pure compound was 143.0-144.0° C.

2. 1,4-Bis-(2-nitro-chalcone) piperazine.

Empirical Formula	$C_{34}H_{32}O_6N_4$
Structural Formula	



Molecular Weight	592.27	
Melting Point	143.0-144.0° C.	
Yield of Crude Product	87%	
Yield after One Recrystallization	80%	
Analysis	Found	Calculated
Nitrogen	9.48%	9.46%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Slightly soluble	
Toluene (Recrystallizing solvent)	Slightly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Fairly soluble	

3. Preparation of 1,4-Bis-(2-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 24.3 grams (0.1 mole) of 2-chloro-chalcone was then added. The total volume of the solution was about 100 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box for three days, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times by dissolving in a minimum amount of boiling toluene and then adding a large amount of heptane; the compound separated out immediately. It is insoluble in commercial heptane, whereas 2-chloro-chalcone, which is the principal impurity, is quite soluble. The compound was washed with ether after the final recrystallization. This yielded almost pure white crystals, which became brownish yellow upon standing in a desiccator. The yield of crude product was 22.9 grams (80% of theoretical) and the yield after three recrystallizations was 8.1 grams (28% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.88% N. Calculated: 4.91% N. The corrected melting point of the pure compound was 110.9-111.5° C.

3. 1,4-Bis-(2-chloro-chalcone) piperazine.

Empirical Formula	$C_{34}H_{32}O_2N_2Cl_2$
Structural Formula	

Molecular Weight	571.17	
Melting Point	110.9-111.3° C.	
Yield of Crude Product	80%	
Yield after Three Recrystallizations	30%	
Analysis	Found	Calculated
Nitrogen	4.88%	4.91%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene	Fairly soluble	
Heptane (recrystallizing solvents)	Insoluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

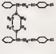
4. Preparation of 1,4-Bis-(4'-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 24.3 grams (0.1 mole) of 4'-chloro-chalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for two hours and then allowed to stand in the ice box two days, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times by dissolving in boiling toluene and then cooling in the ice box. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization, in order to remove the toluene. The yield of crude product was 20.8 grams (73% of theoretical) and the yield after three recrystallizations was 13.5 grams (47% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.88% N. Calculated: 4.91% N. The corrected melting point of the pure compound was 117.7-118.1° C.

4. 1,4-Bis-(4'-chloro-chalcone) piperazine.

Empirical Formula $C_{34}H_{30}O_2N_2Cl_2$

Structural Formula



Molecular Weight	571.17	
Melting Point	117.7-118.1° C.	
Yield of crude Product	73%	
Yield after three Recrystallizations	47%	
Analysis	Found	Calculated
Nitrogen	4.80%	4.91%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

3. Preparation of 1,4-Bis-(4-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 24.3 grams (0.1 mole) of 4-chloro-chalcone was then added. The total volume of the solution was about 175ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box three days, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, fluffy compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 21.2 grams (74% of theoretical) and the yield after three recrystallizations was 12.3 grams (43% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.03% N. Calculated: 4.91% N. The corrected melting point of the pure compound was 146.8-147.0° C.

5. 1,4-Bis-(4-chloro-chalcone) piperazine.

Empirical Formula	$C_{34}H_{32}O_2N_2Cl_2$
Structural Formula	

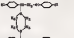
Molecular weight	571.17	
Melting Point	146.0-147.0° C.	
Yield of Crude Product	74%	
Yield after three Recrystallizations	45%	
Analysis	Found	Calculated
Nitrogen	5.05%	4.91%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Fairly soluble	

6. Preparation of 1,4-Bis-(4,4'-dichloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 27.7 grams (0.1 mole) of 4,4'-dichloro-chalcone was then added. The total volume of the solution was about 175 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box three days, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 25.9 grams (81% of theoretical) and the yield after three recrystallizations was 8.6 grams (23% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.48% N. Calculated: 4.38% N. The corrected melting point of the pure compound was 158.4-158.7° C.

6. 1,4-Bis-(4,4'-dichloro-chalcone) piperazine.

Empirical Formula	$C_{34}H_{30}O_2N_2Cl_4$	
Structural Formula		



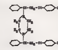
Molecular Weight	640.05	
Melting Point	158.4-158.7° C.	
Yield of Crude Product	81%	
Yield after Three Recrystallizations	55%	
Analysis	Found	Calculated
Nitrogen	4.40%	4.38%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Slightly soluble	
Toluene (Recrystallizing Solvent)	Fairly soluble	
Chloroform	Slightly soluble	
Chlorobenzene	Fairly soluble	

7. Preparation of 1,4-Bis-(4'-bromo-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 28.7 grams (0.1 mole) of 4'-bromo-chalcone was then added. The total volume of the solution was about 170 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with ethanol (95%) and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 25.8 grams (78% of theoretical) and the yield after three recrystallizations was 10.7 grams (33% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.26% N. Calculated: 4.26% N. The corrected melting point of the pure compound was 116.5-117.5° C.

V. 1,4-Bis-(4'-bromo-chalcone) piperazine.

Empirical Formula	$C_{34}H_{32}O_2N_2Br_2$	
Structural Formula		



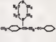
Molecular Weight	660.04	
Melting Point	116.3-117.3° C.	
Yield of Crude Product	70%	
Yield after Three Recrystallizations	35%	
Analysis	Found	Calculated
Nitrogen	4.24%	4.24%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

C. Preparation of 1,4-Bis-(4-methyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 22.2 grams (0.1 mole) of 4-methyl-chalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized four times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 22.8 grams (85% of theoretical) and the yield after four recrystallizations was 3.7 grams (14% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.28% N. Calculated: 5.28% N. The corrected melting point of the pure compound was 145.5-146.0° C.

6. 1,4-Bis-(4-methyl-chalcone) piperazine.

Empirical Formula	$C_{36}H_{38}O_2N_2$	
Structural Formula		



Molecular Weight	530.69	
Melting Point	145.6-146.0° C.	
Yield of Crude Product	83%	
Yield after Four Recrystallizations	14%	
Analysis	Found	Calculated
Nitrogen	5.22%	5.28%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

6. Preparation of 1,4-Bis-(4'-methyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 22.2 grams (0.1 mole) of 4'-methyl-chalcone was then added. The total volume of the solution was about 125 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 23.9 grams (90% of theoretical) and the yield after three recrystallizations was 12.1 grams (46% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.37% N. Calculated, 5.28% N. The corrected melting point of the pure compound was 132.0-133.0° C.

9. 1,4-Bis-(4'-methyl-chalcone) piperazine.

Empirical Formula	$C_{36}H_{38}O_2N_2$
Structural Formula	

Molecular Weight	530.69	
Melting Point	132.0-132.5° C.	
Yield of Crude Product	90%	
Yield after Three Recrystallizations	46%	
Analysis	Found	Calculated
Nitrogen	5.37%	5.28%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Fairly soluble	

13. Preparation of 1,4-Bis-(4-methoxy-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 24.0 grams (0.1 mole) of 4-methoxy-chalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized four times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 24.8 grams (73% of theoretical) and the yield after four recrystallizations was 1.8 grams (5% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.16% N. Calculated; 4.96% N. The corrected melting point of the pure compound was 109.5-110.1° C.

15. 1,4-Bis-(4-methoxy-chalcone) piperazine.

Empirical Formula	$C_{36}H_{38}O_4N_2$
Structural Formula	

Molecular Weight	562.68
Melting Point	129.8-130.1° C.
Yield of Crude Product	75%
Yield after Four Recrystallizations	5%
Analysis	Found Calculated
Nitrogen	5.10% 4.98%
Solubilities	
Water	Insoluble
Ethanol	Insoluble
Ether	Insoluble
Benzene	Fairly soluble
Toluene (Recrystallizing solvent)	Fairly soluble
Chloroform	Very soluble
Chlorobenzene	Soluble

11. Preparation of Di-Bis-(4,4'-dimethyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 23.6 grams (0.1 mole) of 4,4'-dimethyl-chalcone was then added. The total volume of the solution was about 125 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 50% ethanol and then with a large amount of water. It was air-dried and then recrystallized once from about five liters of toluene. This yielded a pure white, fluffy, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 25.7 grams (92% of theoretical) and the yield after one recrystallization was 14.0 grams (50% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.98% N. Calculated: 5.02% N. The corrected melting point of the pure compound was 172.4-173.6° C.

11. 1,4-Bis-(4,4'-dimethyl-chalcone) piperazine.

Empirical Formula	$C_{38}H_{42}O_2N_2$
Structural Formula	

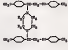
Molecular Weight	558.73
Melting Point	175.4-175.8° C.
Yield of Crude Product	92%
Yield after One Recrystallization	80%
Analysis	Found Calculated
Nitrogen	4.96% 5.02%
Solubilities	
Water	Insoluble
Ethanol	Insoluble
Ether	Insoluble
Benzene	Slightly soluble
Toluene (Recrystallizing solvent)	Slightly soluble
Chloroform	Slightly soluble
Chlorobenzene	Fairly soluble

12. Preparation of 1,4-Bis-(4-methoxy-4'-methyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 25.2 grams (0.1 mole) of 4-methoxy-4'-methylchalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon a white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 22.2 grams (74% of theoretical) and the yield after three recrystallizations was 8.0 grams (27% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.74% N. Calculated: 4.75 % N. The corrected melting point of the pure compound was 149.5-150.0° C.

12. 1,4-Bis-(4-methoxy-4'-methyl-chalcone) piperazine.

Empirical Formula	$C_{38}H_{42}O_4N_2$
Structural Formula	



Molecular Weight	590.33	
Melting Point	149.8-150.8° C.	
Yield of Crude Product	76%	
Yield after Three Recrystallizations	57%	
Analysis	Found	Calculated
Nitrogen	4.76%	4.75%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

13. Preparation of 1,4-Bis-(4-methoxy-4'-bromo-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 31.7 grams (0.1 mole) of 4-methoxy-4'-bromochalcone was then added. The total volume of the solution was about 225 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 22.6 grams (63% of theoretical) and the yield after three recrystallizations was 2.5 grams (7% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 3.82% N. Calculated: 3.89% N. The corrected melting point of the pure compound was 154.0-155.0° C.

13. 1,4-Bis-(4-methoxy-4'-bromo-chalcone) piperazine.

Empirical Formula	$C_{36}H_{36}O_4N_2Br_2$

Structural Formula

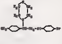
Molecular Weight	720.11	
Melting Point	184.8-186.8° C.	
Yield of Crude Product	65%	
Yield after Three Recrystallizations	7%	
Analysis	Found	Calculated
Nitrogen	3.85%	3.89%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Fairly soluble	

16. Preparation of 1,4-Bis-(4-methyl-4'-bromo-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 30.1 grams (0.1 mole) of 4-methyl-4'-bromo-chalcone was then added. The total volume of the solution was about 150 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized five times from toluene, since yellow crystals of the unreacted chalcone continued to separate out until the fifth recrystallization. This finally yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 29.1 grams (85% of theoretical) and the yield after five recrystallizations was 4.6 grams (13% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.20% N. Calculated: 4.07% N. The corrected melting point of the pure compound was 183.0-185.0° C.

16. 1,4-Bis-(4-methyl-4'-bromo-chalcone) piperazine.

Empirical Formula	$C_{36}H_{36}O_2N_2Br_2$	
Structural Formula		



Molecular weight	688.11	
Melting Point	183.0-183.5° C.	
Yield of crude Product	85%	
Yield after Five Recrystallizations	10%	
Analysis	Found	Calculated
Nitrogen	4.20%	4.07%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Soluble	

15. Preparation of 1,4-Bis-(3-methyl-4'-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 25.7 grams (0.1 mole) of 3-methyl-4'-chloro-chalcone was then added. The total volume of the solution was about 175 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 23.8 grams (79% of theoretical) and the yield after three recrystallizations was 9.6 grams (32% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.69% N. Calculated: 4.68% N. The corrected melting point of the pure compound was 185.6-186.0° C.

15. 1,4-Bis-(2-methyl-4'-chloro-chalcone) piperazine.

Empirical Formula	$C_{36}H_{36}O_2N_2Cl_2$
Structural Formula	

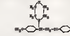
Molecular Weight	599.17	
Melting Point	185.8-186.2° C.	
Yield of Crude Product	75%	
Yield after Three Recrystallizations	50%	
Analysis	Found	Calculated
Nitrogen	4.68%	4.68%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Very soluble	
Chlorobenzene	Soluble	

18. Preparation of 1,4-Bis-(4-methoxy-4'-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 27.3 grams (0.1 mole) of 4-methoxy-4'-chloro-chalcone was then added. The total volume of the solution was about 175 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 85% ethanol and then with a large amount of water. It was air-dried and then recrystallized two times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 26.4 grams (84% of theoretical) and the yield after two recrystallizations was 7.5 grams (24% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.58% N. Calculated: 4.44% N. The corrected melting point of the pure compound was 182.5-183.5° C.

14. 1,4-Bis-(4-methoxy-4'-chloro-chalcone) piperazine.

Empirical Formula	$C_{36}H_{36}O_4N_2Cl_2$
Structural Formula	



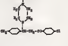
Molecular Weight	631.37	
Melting Point	188.5-189.5° C.	
Yield of Crude Product	84%	
Yield after Two Recrystallizations	24%	
Analysis	Found	Calculated
Nitrogen	4.50%	4.44%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Fairly soluble	

17. Preparation of 1,4-Bis-(4-methyl-4'-chloro-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 25.7 grams (0.1 mole) of 4-methyl-4'-chloro-chalcone was then added. The total volume of the solution was about 200 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 25.1 grams (84% of theoretical) and the yield after three recrystallizations was 6.7 grams (22% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.73% N. Calculated: 4.68% N. The corrected melting point of the pure compound was 148.2-148.8° C.

17. 1,4-Bis-(4-methyl-4'-chloro-chalcone) piperazine.

Empirical Formula	$C_{36}H_{36}O_2N_2Cl$
Structural Formula	



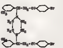
Molecular Weight	599.17	
Melting Point	149.2-149.6° C.	
Yield of Crude Product	84%	
Yield after Three Recrystallizations	28%	
Analysis	Found	Calculated
Nitrogen	4.72%	4.68%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Fairly soluble	
Chlorobenzene	Soluble	

18. Preparation of 1,4-Bis-(2-methyl-4'-bromo-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 30.1 grams (0.1 mole) of 2-methyl-4'-bromochalcone was then added. The total volume of the solution was about 200 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box one day, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 24.6 grams (72% of theoretical) and the yield after three recrystallizations was 6.1 grams (18% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.37% N. Calculated: 4.07% N. The corrected melting point of the pure compound was 128.5-129.5° C.

18. 1,4-Bis-(2-methyl-4'-bromo-chalcone) piperazine.

Empirical Formula	$C_{34}H_{32}O_2N_2Br$
Structural Formula	



Molecular Weight	660.11	
Melting Point	188.8-189.2° C.	
Yield of Crude Product	72%	
Yield after Three Recrystallizations	6%	
Analysis	Found	Calculated
Nitrogen	4.27%	4.24%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Soluble	

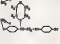
29. 1,4-Bis-(3,4-methylene-dioxy-4'-bromo-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 33.1 grams (0.1 mole) of 3,4-methylene-dioxy-4'-bromo-chalcone was then added. The total volume of the solution was about 170 ml. The solution was refluxed over a free flame for two hours and then allowed to stand in the ice box two days, whereupon a pale yellow, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized by boiling with a large amount of toluene, cooling, and then filtering off the compound. This procedure was necessary since a suitable re-crystallizing solvent could not be found. The chalcone, which is the chief impurity, is quite soluble in toluene. This process yielded a pale tan, crystalline compound. The yield of crude product was 28.4 grams (76% of theoretical) and the yield after purification was 11.6 grams (31% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 3.80% N. Calculated: 3.78% N. The corrected melting point of the pure compound was 184.5-185.2° C.

19. 1,4-Bis-(3,4-methylene-dioxy-4'-bromo-chalcone) piperazine.

Empirical Formula	$C_{36}H_{32}O_6N_2Br_2$

Structural Formula



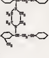
Molecular Weight	748.09	
Melting Point	154.5-155.5° C.	
Yield of Crude Product	78%	
Yield after Purification	81%	
Analysis	Found	Calculated
Nitrogen	3.80%	3.74%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Slightly soluble	
Toluene	Slightly soluble	
Chloroform	Slightly soluble	
Chlorobenzene	Slightly soluble	

30. Preparation of 1,4-Bis-(3-methyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 22.2 grams (0.1 mole) of 3-methyl-chalcone was then added. The total volume of the solution was about 125 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized threetimes from toluene. This yielded a pure, white, crystalline compound. The crystals were washed with ether after the final recrystallization., the yield of crude product was 19.9 grams (75% of theoretical) and the yield after three recrystallizations was 7.4 grams (28% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.33% N. Calculated: 5.28% N. The corrected melting point of the pure compound was 116.0-116.5° C.

28. 1,4-Bis-(3-methyl-chalcone) piperazine.

Empirical Formula	$C_{36}H_{38}O_2N_2$
Structural Formula	



Molecular Weight	530.20	
Melting Point	116.0-116.5° C.	
Yield of Crude Product	75%	
Yield after Three Recrystallizations	30%	
Analysis	Found	Calculated
Nitrogen	5.33%	5.28%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Fairly soluble	

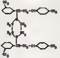
31. Preparation of 1,4-Bis-(3,4'-dimethyl-chalcone) piperazine.

Four and three-tenths grams (0.05 mole) of anhydrous piperazine was dissolved in a minimum amount of boiling toluene under reflux. A hot toluene solution of 23.6 grams (0.1 mole) of 3,4'-dimethyl-chalcone was then added. The total volume of the solution was about 125 ml. The solution was refluxed over a free flame for ten hours and then allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from toluene. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 25.4 grams (91% of theoretical) and the yield after three recrystallizations was 9.5 grams (34% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 5.35% N. Calculated: 5.02% N. The corrected melting point of the pure compound was 165.5-166.5° C.

31. 1,4-Bis-(3,4'-dimethyl-chalcone) piperazine.

Empirical Formula	$C_{38}H_{42}O_2N_2$

Structural Formula



Molecular Weight	558.35	
Melting Point	166.5-168.5° C.	
Yield of Crude Product	61%	
Yield after three Recrystallizations	34%	
Analysis	Found	Calculated
Nitrogen	5.08%	5.02%
Solubilities		
Water	Insoluble	
Ethanol	Insoluble	
Ether	Insoluble	
Benzene	Fairly soluble	
Toluene (Recrystallizing solvent)	Fairly soluble	
Chloroform	Soluble	
Chlorobenzene	Fairly soluble	

B. Negative Reactions with Piperazine

1. Cinnamalacetophenone.

A toluene solution of equimolecular quantities of anhydrous piperazine and cinnamalacetophenone was refluxed for ten hours, and then allowed to stand in the ice box three days. The bright yellow crystals which separated out were recrystallized from alcohol, and mixed melting points proved them to be cinnamalacetophenone.

2. 3,4-Methylene-dioxy-chalcone; (piperonalacetophenone).

A toluene solution of equimolecular quantities of anhydrous piperazine and piperonalacetophenone was refluxed for two hours, and then allowed to stand in the ice box two days. The yellow crystals which separated out were recrystallized from alcohol three times, and mixed melting points proved them to be piperonalacetophenone.

3. 3-Nitro-chalcone.

A toluene solution of equimolecular quantities of anhydrous piperazine and 3-nitro-chalcone was refluxed for ten hours, and then allowed to stand in the ice box two days. A black, tarry mass separated out, and was not further investigated.

4. Mesityl oxide.

Anhydrous piperazine and varying amounts of mesityl oxide were refluxed in various solvents such as benzene, toluene, and 95% ethanol, as well as without a solvent. Varying amounts of sodium hydroxide were tried with the alcoholic solution. In all cases, unreacted piperazine seperated out, and was detected by preparing the dinitroso derivative and determining mixed melting points with an authentic sample.

C. Addition Compounds of Morpholine.

1. Preparation of 4-chalcone morpholine.

Forty-one and six-tenths grams (0.2 mole) of chalcone was dissolved in about 175 ml. of boiling, commercial heptane under reflux. Twenty-six and one-tenth grams (0.3 mole = 0.1 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was then allowed to stand in the ice box one day, whereupon the pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from commercial heptane. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 54.8 grams (93% of theoretical) and the yield after three recrystallizations was 40.2 grams (68% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.81% N. Calculated: 4.75% N. The corrected melting point of the pure compound was 80.5-81.0° C.

1. 4-Chalcone morpholine.

Empirical formula	$C_{19}H_{21}O_2N$
Structural formula	

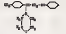
Molecular Weight	295.37	
Melting Point	80.5-81.0° C.	
Yield of Crude Product	92%	
Yield after Three Recrystallizations	68%	
Analysis	Found	Calculated
Nitrogen	4.81%	4.74%
Solubilities		
Water	Insoluble (dec. hot)	
Ethanol	Very soluble	
Ether	Very soluble	
Isopropyl ether	Fairly soluble	
Heptane (Recrystallizing solvent)	Fairly soluble	
Toluene	Very soluble	
Chloroform	Very soluble	
Acetone	Very soluble	
Dilute HCl	Soluble	

G. Preparation of 4-(4-methyl-chalcone) morpholine.

Forty-four and four-tenths grams (0.2 mole) of 4-methyl-chalcone was dissolved in about 200 ml. of boiling, commercial heptane under reflux. Twenty-six and one tenth grams (0.3 mole = 0.1 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was then allowed to stand in the ice box two days, whereupon the pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from commercial heptane. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 58.3 grams (94% of theoretical) and the yield after three recrystallizations was 53.0 grams (86% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.70%. Calculated: 4.53% N. The corrected melting point of the pure compound was 88.0-90.8° C.

9. 4-(4-Methyl-chalcone) morpholine.

Empirical Formula	$C_{20}H_{23}O_2N$
Structural Formula	



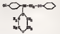
Molecular Weight	309.38	
Melting Point	99.0-99.5° C.	
Yield of Crude Product	94%	
Yield after Three Recrystallizations	86%	
Analysis	Found	Calculated
Nitrogen	4.70%	4.53%
Solubilities		
Water	Insoluble (dec. hot)	
Ethanol	Very soluble	
Ether	Very soluble	
Isopropyl ether	Very soluble	
Heptane (Recrystallizing solvent)	Fairly soluble	
Toluene	Very soluble	
Chloroform	Very soluble	
Acetone	Very soluble	
Dilute HCl	Soluble	

B. Preparation of 4-(4-chloro-chalcone) morpholine.

Twelve and one-tenth grams (0.05 mole) of 4-chloro-chalcone was dissolved in about 100 ml. of boiling, commercial heptane under reflux. Eight and seven-tenths grams (0.1 mole = 0.05 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from commercial heptane. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 15.6 grams (94% of theoretical) and the yield after three recrystallizations was 11.0 grams (67% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.28% N. Calculated: 4.25% N. The corrected melting point of the pure compound was 89.5-90.0° C.

3. 4-(4-Chloro-chalcone) morpholine.

Empirical Formula	$C_{19}H_{20}O_2NCl$
Structural Formula	



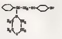
Molecular Weight	329.82	
Melting Point	89.5-90.0° C.	
Yield of Crude Product	94%	
Yield after Three Recrystallizations	67%	
Analysis	Found	Calculated
Nitrogen	4.28%	4.25%
Solubilities		
Water	Insoluble (dec. hot)	
Ethanol	Soluble	
Ether	Very soluble	
Isopropyl ether	Very soluble	
Heptane (Recrystallizing solvent)	Fairly soluble	
Toluene	Very soluble	
Chloroform	Very soluble	
Acetone	Very soluble	
Dilute HCl	Soluble	

6. Preparation of 4-(4'-bromo-chalcone) morpholine.

Nine grams (0.031 mole) of 4'-bromo-chalcone was dissolved in about 100 ml. of boiling, commercial heptane under reflux. Five and four-tenths grams (0.062 mole = 0.031 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized three times from commercial heptane. This yielded very heavy, white crystals. The crystals were washed with ether after the final recrystallization. The yield of crude product was 11.0 grams (95% of theoretical) and the yield after three recrystallizations was 8.9 grams (77% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 3.74% N. Calculated; 3.74% N. The corrected melting point of the pure compound was 95.0-95.5° C.

4. 4-(4'-Bromo-chalcone) morpholine.

Empirical Formula	$C_{19}H_{20}O_2NBr$
Structural Formula	



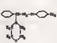
Molecular Weight	374.08	
Melting Point	99.0-99.8° C.	
Yield of Crude Product	86%	
Yield after Three Recrystallizations	77%	
Analysis	Found	Calculated
Nitrogen	3.70%	3.74%
Solubilities		
Water	Insoluble (dec. hot)	
Ethanol	Soluble	
Ether	Soluble	
Isopropyl ether	Soluble	
Heptane (Recrystallizing solvent)	Fairly soluble	
Toluene	Very soluble	
Chloroform	Very soluble	
Acetone	Very soluble	
Dilute HCl	Very soluble	

8. Preparation of 4-(4'-methyl-chalcone) morpholine.

Twenty-two and two-tenths grams (0.1 mole) of 4'-methyl-chalcone was dissolved in about 100 ml. of boiling, commercial heptane under reflux. Thirteen and one-tenth grams (0.15 mole = 0.05 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was allowed to stand in the ice box two days, whereupon the almost pure white, crystalline compound separated out. The compound was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was airdried and then recrystallized three times from commercial heptane. This yielded a pure white, crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 29.1 grams (94% of theoretical) and the yield after three recrystallizations was 22.8 grams (74% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 4.50% N. Calculated: 4.53% N. The corrected melting point of the pure compound was 89.0-90.5° C.

8. 4-(4'-Methyl-chalcone) morpholine.

Empirical Formula	$C_{20}H_{23}O_2N$
Structural Formula	



Molecular Weight	309.18
Melting Point	90.0-90.8° C.
Yield of Crude Product	94%
Yield after Three Recrystallizations	76%
Analysis	Found Calculated
Nitrogen	4.50% 4.53%
Solubilities	
Water	Insoluble (dec. hot)
Ethanol	Soluble
Ether	Very soluble
Isopropyl ether	Very soluble
Heptane (Recrystallizing solvent)	Fairly soluble
Toluene	Very soluble
Chloroform	Very soluble
Acetone	Very soluble
Dilute HCl	Soluble

6. Preparation of 4,4'-(dibenzalacetone)-bis-morpholine.

Eleven and seven-tenths grams (0.05 mole) of dibenzalacetone was dissolved in about 100 ml. of boiling, commercial heptane under reflux. Thirteen and one-tenth grams (0.15 mole = 0.05 mole excess) of anhydrous morpholine was then added, and the solution refluxed over a free flame for ten hours. It was then allowed to stand in the ice box nine days, whereupon the almost pure white, crystalline compound separated out, and the pale yellow oil which first separated out solidified. The whole mass was filtered with suction, washed with a small amount of 95% ethanol and then with a large amount of water. It was air-dried and then recrystallized six times from commercial heptane. This yielded an almost pure white (very pale tan), crystalline compound. The crystals were washed with ether after the final recrystallization. The yield of crude product was 20.1 grams (99% of theoretical) and the yield after six recrystallizations was 16.1 grams (80% of theoretical). The purified product was dried in vacuo over concentrated sulfuric acid before being subjected to analysis. When analyzed for nitrogen it gave 6.88% N. Calculated; 6.86% N. The corrected melting point of the pure compound was 99.6-100.2° C.

6. 4,4'-(Dibenzalacetone)-bis-morpholine.

Empirical Formula	$C_{25}H_{32}O_3N_2$
Structural Formula	

Molecular Weight	408.27
Melting Point	99.6-100.2° C.
Yield of Crude Product	86%
Yield after Six Recrystallizations	35%
Analysis	Found Calculated
Nitrogen	6.88% 6.86%
Solubilities	
Water	Insoluble (Dec. hot)
Ethanol	Soluble
Ether	Soluble
Isopropyl ether	Soluble
Heptane (Recrystallizing solvent)	Fairly soluble
Toluene	Very soluble
Chloroform	Very soluble
Acetone	Very soluble
Dilute HCl	Very soluble

D. Negative Reactions with Morpholine

1. 4-Methoxy-4'-bromo-chalcone.

A commercial heptane solution of 0.05 mole of 4-methoxy-4'-bromo-chalcone and 0.055 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box two days. The yellow crystals which separated out were recrystallized from commercial heptane, and mixed melting points proved them to be the unreacted chalcone.

2. 4-Methoxy-4'-chloro-chalcone.

A commercial heptane solution of 0.05 mole of 4-methoxy-4'-chloro-chalcone and 0.1 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box two days. The yellow crystals which separated out were recrystallized from commercial heptane, and mixed melting points proved them to be the unreacted chalcone.

3. 4-Methyl-4'-bromo-chalcone.

A commercial heptane solution of 0.05 mole of 4-methyl-4'-bromo chalcone and 0.055 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box ten days. The yellow crystals which separated out were recrystallized from commercial heptane, and mixed melting points proved them to be the unreacted chalcone.

4. Cinnamalacetophenone.

A commercial heptane solution of 0.05 mole of cinnamalacetophenone and 0.1 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box one day. The bright yellow crystals which separated out were recrystallized from 95% ethanol, and mixed melting points proved them to be the unreacted cinnamalacetophenone.

5. 4-Methyl-4'-bromo-chalcone.

A commercial heptane solution of 0.08 mole of 4-methyl-4'-bromo-chalcone and 0.085 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box two days. The yellow crystals which separated out were recrystallized from commercial heptane, and mixed melting points proved them to be the unreacted chalcone.

6. 4,4'-Dimethyl-chalcone.

A commercial heptane solution of 0.1 mole of 4,4'-dimethyl-chalcone and 0.15 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box two days. The almost pure white crystals which separated out were recrystallized two times from commercial heptane, yielding pale yellow crystals. Mixed melting points proved them to be the chalcone. Apparently the addition compound is too unstable to be isolated in the pure state.

7. 4,4'-Dichloro-chalcone.

A commercial heptane solution of 0.058 mole of 4,4'-dichloro-chalcone and 0.1 mole of morpholine was refluxed for ten hours, and then allowed to stand in the ice box two days. The almost pure white crystals which separated out were recrystallized three times from commercial heptane, yielding pale yellow crystals. Mixed melting points proved them to be the chalcone, resulting from the unstable addition.

PREPARATION OF INTERMEDIATES

1. Chalcone; benzalacetophenone.

The Eastman product, melting point 55-57° C. was used in this research.

Benzalacetophenone is prepared readily by dissolving equimolecular quantities of benzaldehyde and acetophenone in 95% ethanol and adding 100 grams of a 10% aqueous solution of sodium hydroxide per mole of aldehyde (or ketone). The compound may be recrystallized from 95% ethanol. A detailed procedure is give by Gilman[27].

2. 3-Nitro-chalcone.

Thirty and two-tenths grams (0.2 mole) of m-nitro-benzaldehyde and 24.0 grams (0.2 mole) of acetophenone were dissolved in about 700 ml. of warm 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon it became solid almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from benzene, yielding pale yellow crystals. The yield after three recrystallizations was 31.9 grams (63% of theoretical). The corrected melting point of the pure product was 142.8-143.0° C. The melting point reported in the literature[28] is 146°; 145-146° C.

5. 2-Chloro-chalcone.

Forty-six and eight-tenths grams (0.3 mole) of o-chloro-benzaldehyde and 40.0 grams (0.3 mole) of acetophenone were dissolved in about 350 ml. of 95% ethanol. Thirty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. The crystals were filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from 95% ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 57.0 grams (70% of theoretical). The corrected melting point of the pure product was 50.0-51.0° C.

6. 4'-Chloro-chalcone.

Twenty-one and two-tenths grams (0.2 mole) of benzaldehyde and 30.9 grams (0.2 mole) of p-chloroacetophenone were dissolved in about 125 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow compound separated out almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized twice from 95% ethanol, yielding pale yellow crystals. The yield after two recrystallizations was 38.8 grams (80% of theoretical). The corrected melting point of the pure product was 96.0-98.0° C.

4'-Chloro-chalcone has been prepared by adding a methanol solution of the aldehyde and ketone to an ethanol solution of sodium ethylate[29]. Chloroform or diethyl ether was used as a recrystallizing solvent. This research has shown that the compound is too soluble in these solvents to make their use feasible. The above reference reports the melting point to be 101°.

5. 4-Chloro-chalcone.

Thirty-five and one-tenth grams (0.25 mole) of p-chloro-benzaldehyde and 30.0 grams (0.25 mole) of acetophenone were dissolved in about 200 ml. of 95% ethanol. Twenty-five grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon it became solid almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from 95% ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 35.0 grams (58% of theoretical). The corrected melting point of the pure compound was 112.5-113.5° C; the melting point reported in the literature[30] is 103-104° C.

6. 4,4'-Dichloro-chalcone.

Forty-two grams (0.3 mole) of p-chlorobenzaldehyde and 46.4 grams (0.3 mole) of p-chloroacetophenone were dissolved in about 450 ml. of 95% ethanol. Thirty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from ethyl acetate, yielding pale yellow leaflets. The yield after three recrystallizations was 63.7 grams (77% of theoretical). The corrected melting point of the pure compound was 155.0-156.0° C. The melting point reported in the literature[31] is 156-157° C.

7. 4'-Bromo-chalcone.

Twenty-one and two-tenths grams (0.2 mole) of benzaldehyde and 39.8 grams (0.2 mole) of p-bromoacetophenone were dissolved in about 300 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from 95% ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 40.0 grams (70% of theoretical). The corrected melting point of the pure compound was 103.5-104.0° C. The melting points recorded in the literature are varying. Dilthey, et al.[32], report it to be 104-105° C.; Heritage and Barnley[33], report it as 100-101° C.

8. 4-Methyl-chalcone.

Forty grams (0.3 mole) of p-tolualdehyde and 40.0 grams (0.3

mole) of acetophenone were dissolved in about 375 ml. of 95% ethanol. Thirty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized once from commercial heptane, yielding pale yellow crystals. The yield after was recrystallization was 52.0 grams (70% of theoretical). The corrected melting point of the pure compound was 95.5-96.5° C. The melting point reported in the literature[34] is 96.5° C.

9. 4'-Methyl-chalcone.

Fifty-three grams (0.5 mole) of benzaldehyde and 67.0 grams (0.5 mole) of p-methyl-acetophenone were dissolved in about 125 ml. of 95% ethanol. Fifty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was thoroughly stirred and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from dilute ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 65.9 grams (59% of theoretical). The corrected melting point of the pure compound was 71.5-72.5° C. The melting point reported in the literature is 59-60°; 77° C.[34].

10. 4-Methoxy-chalcone.

Sixty-eight grams (0.5 mole) of anisaldehyde and 60.0 grams (0.5 mole) of acetophenone were dissolved in about 500 ml. of 95% ethanol. Fifty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from 95% ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 97.0 grams (82% of theoretical). The corrected melting point of the pure compound was 73.5-74.0° C. The melting point reported in the literature[35] is 77-78° C.

11. 4,4'-Dimethyl-chalcone.

Twenty-four grams (0.2 mole) of p-tolualdehyde and 26.8 grams (0.2 mole) of p-methyl-acetophenone were dissolved in about 125 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. It was allowed to stand in the ice box one day, filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from 95% ethanol, yielding pale yellow crystals. The yield after three recrystallizations was 30.9 grams (65% of theoretical). The corrected melting point of the pure compound was 127.5-128.0° C.

12. 4-Methoxy-4'-methyl-chalcone.

Twenty-seven and two-tenths grams (0.2 mole) of anisaldehyde and 26.8 grams (0.2 mole) of p-methyl-acetophenone were dissolved in about 250 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized once from 95% ethanol, yielding pale yellow crystals. The yield after one recrystallization was 28.0 grams (56% of theoretical). The corrected melting point of the pure compound was 96.5-97.0° C.

13. Cinnamalacetophenone.

Forty-eight and eight-tenths grams (0.37 mole) of cinnamic aldehyde and 44.4 grams (0.37 mole) of acetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was thoroughly stirred and then allowed to stand in the ice box one day, whereupon the bright yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water and air-dried. The compound was recrystallized three times from 95% ethanol, yielding bright yellow crystals. The yield after three recrystallizations was 50.0 grams (58% of theoretical). The corrected melting point of the pure product was 100.0-101.0° C. The melting point reported in the literature[26] is 102-103° C.

14. 4-Methoxy-4'-bromo-chalcone.

Twenty-seven and two-tenths grams (0.2 mole) of anisaldehyde and 40.0 grams (0.2 mole) of p-bromacetophenone were dissolved in about 160 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, and the pale yellow, crystalline compound separated out almost immediately. The compound was allowed to stand in the ice box one day, then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized once from a large amount of commercial heptane, yielding pale yellow crystals. The yield after one recrystallization was 59.2 grams (93% of theoretical). The corrected melting point of the pure compound was 144.0-145.5° C.

15. 4-Methyl-4'-bromo-chalcone.

Twenty-four grams (0.2 mole) of p-tolualdehyde and 40.0 grams (0.2 mole) of p-bromacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly and then allowed to stand in the ice box one day, whereupon the pale yellow, crystalline compound separated out. It was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized once from a large amount of commercial heptane, yielding pale yellow crystals. The yield after one recrystallization was 50.0 grams (83% of theoretical). The corrected melting point of the pure compound was 162.0-162.4° C.

16. 3-Methyl-4'-chloro-chalcone.

Twenty-four grams (0.2 mole) of m-tolualdehyde and 31.0 grams (0.2 mole) of p-chloroacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly; whereupon the pale yellow, crystalline compound separated out almost immediately. The compound was allowed to stand in the ice box one day, then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from a small amount of commercial heptane, yielding pale yellow crystals. The yield after three recrystallizations was 37.2 grams (73% of theoretical). The corrected melting point of the pure compound was 105.5-106.0° C.

17. 4-Methoxy-4'-chloro-chalcone.

Twenty-seven and two-tenths grams (0.2 mole) of anisaldehyde and 31.0 grams (0.2 mole) of p-chloroacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. The compound was allowed to stand in the ice box one day, then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from a large amount of commercial heptane, yielding pale yellow, fluffy needles. The yield after three recrystallizations was 45.7 grams (84% of theoretical). The corrected melting point of the pure compound was

121.5-122.0° C.

18. 4-Methyl-4'-chloro-chalcone.

Twenty-four grams (0.2 mole) of p-tolualdehyde and 31.0 grams (0.2 mole) of p-chloroacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. The compound was allowed to stand in the ice box one day, then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized two times from a large amount of commercial heptane, yielding pale yellow needles. The yield after two recrystallizations was 37.0 grams (72% of theoretical). The corrected melting point of the pure compound was 158.8-159.4° C.

19. 3-Methyl-4'-bromo-chalcone.

Twenty-four grams (0.2 mole) of m-tolualdehyde and 40.0 grams (0.2 mole) of p-bromoacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the pale yellow, crystalline compound separated out almost immediately. The compound was allowed to stand in the ice box one day, then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from commercial heptane, yielding pale yellow crystals. The yield after three recrystallizations was 43.4 grams (78% of theoretical). The corrected melting point of the pure compound was 114.5-115.5° C.

20. 3,4'-Dimethyl-chalcone.

Twenty-four grams (0.2 mole) of m-tolualdehyde and 26.8 grams (0.2 mole) of p-methyl-acetophenone were dissolved in about 100 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the compound separated out almost immediately in the form of an oil. The solution was allowed to stand in the ice box one day and the oil changed to pale yellow crystals. The compound was then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from a small amount of commercial heptane, yielding pale yellow crystals. The yield after three recrystallizations was 38.2 grams (86% of theoretical). The corrected melting point of the pure compound was 72.5-73.0° C.

21. 3-Methyl-chalcone.

Forty-eight grams (0.4 mole) of m-tolualdehyde and 48.0 grams (0.4 mole) of acetophenone were dissolved in about 200 ml. of 95% ethanol. Forty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the compound separated out almost immediately in the form of an oil. The solution was allowed to stand in the ice box one day and the oil changed to pale yellow crystals. The compound was then filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized three times from a small amount of commercial heptane, yielding pale yellow crystals. The yield after three recrystallizations was 20.3 grams (86% of theoretical). The corrected melting point of the pure compound was 85.0-86.0° C.

32. 3,4-Methylene-dioxy-chalcone; piperonalacetophenone.

Fifty grams (0.2 mole) of piperonal and 40.0 grams (0.3 mole) of acetophenone were dissolved in about 375 ml. of 95% ethanol. Thirty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon the yellow, crystalline compound separated out almost immediately., The solution was allowed to stand in the ice box one day, and the compound was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized one time from 95% ethanol, yielding yellow crystals. The yield after one recrystallization was 30.0 grams (60% of theoretical). The corrected melting point of the pure compound was 121.5-121.6° C. The melting point reported in the literature[37] is 122° C.

33. 3,4-Methylene-dioxy-4'-bromo-chalcone.

Thirty grams (0.2 mole) of piperonal and 40.2 grams (0.2 mole) of p-bromoacetophenone were dissolved in about 150 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was thoroughly stirred, whereupon the pale yellow, crystalline compound separated out almost immediately. The solution was allowed to stand in the ice box one day, and the compound was filtered with suction, washed with a large amount of water, and air-dried. The compound was recrystallized two times from about four liters of commercial heptane, yielding pale yellow crystals. The yield after one recrystallization was 58.4 grams (83% of theoretical). The corrected melting point of the pure compound was 138.0-138.5° C.

84. 2-Nitro-chalcone.

Thirty and two-tenths grams (0.2 mole) of o-nitro-benzaldehyde and 24.0 grams (0.2 mole) of acetophenone were dissolved in about 200 ml. of 95% ethanol. Twenty grams of a 10% aqueous solution of sodium hydroxide was then added. The solution was stirred thoroughly, whereupon a dark brown compound separated out almost immediately. The solution was allowed to stand in the ice box one day, and then filtered with suction. The dark-brown crystals were washed with water, air-dried, and recrystallized three times from alcohol; the alcoholic solution was boiled with 'norite' during the first recrystallization. This yielded fluffy, orange crystals. The yield after three recrystallizations was 15.3 grams (30% of theoretical). The corrected melting point of the pure compound was 123.5-125.0° C.

85. Dibenzalacetone.

The procedure used is that given in 'Organic Syntheses'[86].

A mixture of 106 grams (1 mole) of benzaldehyde and 29 grams (0.5 mole) of acetone is added, with mechanical stirring, to a cooled solution of 100 grams of sodium hydroxide in 1000 ml. of water and 800 ml. of 95% ethanol. The mixture is stirred for about one hour, and the mush is then filtered with suction and washed with a large amount of water. The product was air-dried and then recrystallized two times from ethyl acetate, yielding bright yellow crystals. The yield after two recrystallizations was 65.0 grams (56% of theoretical). The corrected melting point of the pure compound was 110.0-111.6° C.

SUMMARY

1. The following new addition compounds of piperazine with chalcones have been prepared and studied:

		Page
(1.)	1,4-Bis-chalcone piperazine	23
(2.)	1,4-Bis-(3-nitro-chalcone) piperazine	25
(3.)	1,4-Bis-(2-chloro-chalcone) piperazine	27
(4.)	1,4-Bis-(4'-chloro-chalcone) piperazine	29
(5.)	1,4-Bis-(4-chloro-chalcone) piperazine	31
(6.)	1,4-Bis-(4,4'-dichloro-chalcone) piperazine	33
(7.)	1,4-Bis-(4'-bromo-chalcone) piperazine	35
(8.)	1,4-Bis-(4-methyl-chalcone) piperazine	37
(9.)	1,4-Bis-(4'-methyl-chalcone) piperazine	39
(10.)	1,4-Bis-(4-methoxy-chalcone) piperazine	41
(11.)	1,4-Bis-(4,4'-dimethyl-chalcone) piperazine	43
(12.)	1,4-Bis-(4-methoxy-4'-methyl-chalcone) piperazine	45
(13.)	1,4-Bis-(4-methoxy-4'-bromo-chalcone) piperazine	47
(14.)	1,4-Bis-(4-methyl-4'-bromo-chalcone) piperazine	49
(15.)	1,4-Bis-(3-methyl-4'-chloro-chalcone) piperazine	51
(16.)	1,4-Bis-(4-methoxy-4'-chloro-chalcone) piperazine	53
(17.)	1,4-Bis-(4-methyl-4'-chloro-chalcone) piperazine	55
(18.)	1,4-Bis-(3-methyl-4'-bromo-chalcone) piperazine	57
(19.)	1,4-Bis-(3,4-methylene-dioxy-4'-bromo-chalcone) piperazine	59
(20.)	1,4-Bis-(3-methyl-chalcone) piperazine	61
(21.)	1,4-Bis-(3,4'-dimethyl-chalcone) piperazine	63.

2. The following alpha, beta-unsaturated ketones were not successfully reacted with piperazine under conditions which were successful with the foregoing compounds;

		Page
(1.)	Cinnamalacetophenone	65
(2.)	3,4-Methylene-dioxy-chalcone; Piperonalacetophenone	65
(3.)	2-Nitro-chalcone	66
(4.)	Mesityl oxide	66

3. The following new addition compounds of morpholine with alpha, beta-unsaturated ketones have been prepared and studied;

(1.)	4-Chalcone morpholine	67
(2.)	4-(4-Methyl-chalcone) morpholine	68
(3.)	4-(4-Chloro-chalcone) morpholine	71
(4.)	4-(4'-Bromo-chalcone) morpholine	73
(5.)	4-(4'-Methyl-chalcone) morpholine	75
(6.)	4,4'-(Dibenzalacetone)-bis-morpholine	77

4. The following alpha, beta-unsaturated ketones were not successfully reacted with morpholine, or could not be isolated, under conditions which were successful with the foregoing compounds;

(1.)	4-Methoxy-4'-bromo-chalcone	79
(2.)	4-Methoxy-4'-chloro-chalcone	79
(3.)	4-Methyl-4'-bromo-chalcone	79
(4.)	Cinnamalacetophenone	79
(5.)	4-Methyl-4'-chloro-chalcone	80
(6.)	4,4'-Dimethyl-chalcone	80

		Page
(7.)	4,4'-Dichloro-chalcone	80

6. The following alpha, beta-unsaturated ketones have been prepared and corrected physical data reported;

(1.)	Chalcone; Benzalacetophenone	81
(2.)	3-Nitro-chalcone	81
(3.)	2-Chloro-chalcone	82
(4.)	4'-Chloro-chalcone	83
(5.)	4-Chloro-chalcone	83
(6.)	4,4'-Dichloro-chalcone	83
(7.)	4'-Bromo-chalcone	84
(8.)	4-Methyl-chalcone	84
(9.)	4'-Methyl-chalcone	85
(10.)	4-Methoxy-chalcone	85
(11.)	4,4'-Dimethyl-chalcone	86
(12.)	4-Methoxy-4'-methyl-chalcone	87
(13.)	Cinnamalacetophenone	87
(14.)	4-Methoxy-4'-bromo-chalcone	88
(15.)	4-Methyl-4'-bromo-chalcone	88
(16.)	3-Methyl-4'-chloro-chalcone	89
(17.)	4-Methoxy-4'-chloro-chalcone	89
(18.)	4-Methyl-4'-chloro-chalcone	90
(19.)	3-Methyl-4'-bromo-chalcone	90
(20.)	3,4-Dimethyl-chalcone	91
(21.)	3-Methyl-chalcone	91

ACKNOWLEDGMENTS

The author expresses his sincere appreciation to Dr. C.B. Pollard, Chairman of the author's Supervisory Committee, who has directed this research. The success of the undertaking is due largely to Dr. Pollard's kindness and constructive criticism.

The author desires to thank his fellow associates also for their many suggestions and advice, and especially Dr. J.P. Bain, who instigated the study of conjugate systems in this laboratory. To the entire faculty the author wishes to express his appreciation for the many pleasant associations which have added much to the enjoyment of the work.

BIBLIOGRAPHY

1. Michael, J. prakt. Chem. (2) 37, 524 (1888); 60, 286, 409 (1899); 68, 487 (1903); Ber., 39, 2138 (1906)
2. Vorlander and Mumme, Ber. 36, 1470 (1903)
3. Vorlander and Hayakawa, Ber., 36, 3528 (1903)
4. Vorlander, Ann. 341, 1 (1905); 345, 198 (1906)
5. Thiele, Ann. 306, 87 (1899)
6. Griner, Compt. rend. 116, 723 (1893); 117, 553 (1893)
7. Thiele, Ann. 308, 337 (1899)
8. Willstatter and Bruce, Ber. 40, 3979 (1907)
9. Farmer, Lawrence and Thorpe, J. Chem. Soc. 729 (1928)
10. Harries and Lellman, Ber. 30, 230, 2726 (1897)
11. Harries and Jablonski, Ber. 31, 1371 (1898)
12. Harries, Ann. 330, 161 (1904)
13. Lapworth, J. Chem. Soc. 73, 445 (1898)
14. Kuhn, 4th Solvay Report (1931)
15. Kuhn and Winterstein, Helv. Chim. Acta. 11, 87 (1928)
16. Lowry, J. Chem. Soc. 123, 824 (1923)
17. Waters, Physical Aspects of Organic Chemistry, pp. 363-364
18. Robinson, J. Chem. Soc. 109, 1039 (1916)
19. Decker, Ber. 37, 583 (1904); 38, 2493 (1905)
20. Robinson, Solvay Reports (1931)
21. Nef, Ann. 298, 202 (1898)
22. Bauer, Ber. 37, 3488 (1904)

23. Moser, J. pr. Chem. (2) 78, 201 (1908)

24. Bauer and Moser, Ber. 40, 918 (1907)

25. Tauber and Wildi, Ber. 31, 349 (1898)

26. Georgi and Schwyzer, J. prakt. Chem. 86 (2), 273 (1912);

cf. C.A. 7, 2129 (1913)

27. Gilman, Organic Syntheses, Collective Vol. I, pp. 71-72

28. Beilstein, 7, 428

29. Dilthey, et al., J. prakt. Chem. 101, 177-202;

cf. C.A. 15, 1291 (1921)

30. Beilstein, 7 , 421

31. Straus and Ackermann, Ber. 42, 1812 (1909)

32. Dilthey, et al., J. prakt. Chem. 101 177 (1921)

33. Heritage and Barnley, Am. Chem. J. 44, 69 (1910)

34. Beilstein, 7, 420

35. Beilstein, 8, 128

36. Beilstein, 7, 429

37. Beilstein, 10, 141

38. Whitmore, Organic Syntheses, Vol. 12, pp. 22-26

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COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee, and has been approved by all members of the Committee. It was submitted to the graduate council and was approved as partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

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